DETAILED ACTION

Claims 10, 12-13 and 28 are currently pending and under consideration. Claims 1-9 and 14-27 were canceled and claim 28 was added in the claim amendments received August 18, 2009. Claim 11 was cancelled in the amendments received March 22, 2011.

Election/Restrictions

Applicant's elected Group 5, claims 10-13, without traverse in the reply filed on August 18, 2009.

Applicant's elected species of detecting a transcriptome, quantitative PCR, disease state, cancer of the oral cavity, and biomarker, IL-8, without traverse in the reply filed on August 18, 2009.

Withdrawn Rejections

The rejection of Claims 10-13 and 28 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the claim amendments.

The rejection of Claims 10-13 and 28 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the claim amendments.

The rejection of Claim 10 under 35 U.S.C. 102(b) as being anticipated by Gocke et al. (US Patent 6511805, granted January 28, 2003) is withdrawn in view of the claim amendments.

The provisional rejection of Claims 10, 13, and 28 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4, 7-12, 14, 15, 17, and 20 of copending Application No. 12/468766 is withdrawn in view of the claim amendments.

The provisional rejection of Claim10 and 28 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, and 7-10 of copending Application No. 12/457347 is withdrawn in view of the claim amendments.

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, 12-13 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of screening for gene expression in saliva, the specification does not provide sufficient guidance for diagnosing cancer of the oral cavity and/or oropharynx. The specification does not enable a person skilled in the art to make and use the invention commensurate in scope with the claim. This is a **scope of enablement** rejection. Modifications to the rejection were necessitated by the claim amendments for clarification.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to:

1. The breadth of the claims;
2. The nature of the invention;

3. The state of the prior art;
4. The level of skill in the art;
5. The level of predictability in the art;
6. The amount of direction provided by the inventor;
7. The presence or absence of working examples;
8. The quantity of experimentation necessary needed to make or use the invention based on the disclosure.

See *In re Wands* USPQ 2d 1400 (CAFC 1988):

The breadth of the claims and the nature of the invention:

The present invention is drawn to a method for diagnosing an oral or systemic pathology, disease, or disorder in a subject comprising detecting, in a cell free saliva fluid phase of a subject, an "mRNA profile" of a gene associated with the pathology, disease, or disorder, and comparing the RNA profile of the gene with a predetermined mRNA profile of the gene. The invention as claimed encompasses any cancer of the oral cavity or oropharynx and diagnosis of the disorder using any single gene.

Although addressing the method of correlating gene expression levels in subjects known to have oral squamous cell carcinoma (OSCC), the specification does not provide sufficient guidance for diagnosing any cancer, or oral cancer, in an unknown sample. The specification also does not address diagnosing any cancer with a single gene. Specifically, the specification provides data regarding expression levels of select genes in subjects having OSCC compared to normal subjects, however the specification does not provide data regarding diagnosing an unknown subject, or using the gene expression levels to differentiate any unknown subjects, with any disease or cancer of the oral cavity or oropharynx, from any other subjects. In fact, the specification provides no data regarding differentiating any subject with OSCC from any other subject using a single gene. There are no specific examples or data demonstrating diagnosis of

any cancer, or any cancer of the oral cavity or oropharynx, by correlating with gene expression. The specification also provides no specific examples of diagnosing OSCC by correlating with gene expression of a single gene. The specification merely teaches correlating changes in gene expression form subjects known to have OSCC. Accordingly, the claim scope is unduly broad with respect to the encompassed method of diagnosing an oral or systemic pathology, disease, or disorder in a subject, including cancer of the oral cavity or oropharynx.

The state of the prior art and the level of predictability in the art:

Diagnosis of cancer (or oral cancer/OSCC) by correlating with gene expression is highly unpredictable in the art. Not all subjects have the same altered gene expression and have alterations in different genes. For example, Sun et al. (Gene expression profiling on lung cancer outcome prediction: present clinical value and future premise, 2006, Cancer Epidemiol Biomarkers Prev, Vol 15, pp 2063-2068) teach that while gene expression data and microarray analysis show promise as analytical tools, its clinical applications are still questionable (see p 2066, col 1, last para through col 2, first para). Sun et al. further list various issues that arise in application of microarray data in clinical settings:

> "Reasons include the following: (a) There is a significant overlap for clinical outcome prediction between gene expression profiles and pathologic features, and most studies have not shown a superior performance using the new technology over conventional predictors, particularly when evaluated collectively. (b) Most studies had a limited number of cases and an independent validation was not adequately conducted. (c) Current analytic algorithms favor genes at high expression or genes highly differentially expressed, most of which are related to tumor differentiation and may not correlate with clinical outcomes; conversely, genes expressed at low levels or in a subtle difference are often overlooked, which may be quite relevant biologically to clinical questions. (d) There are still some unsolved technical issues about DNA microarray; for example, different microarray platforms (27) or studies from different laboratories using the same platform (28) often produce inconsistent results even when the same RNA samples were used for hybridization. (e) Results from different analytic approaches also differ (23). As

> an undesirable consequence, consistent or overlapped genes selected for predicting the same outcome from multiple studies are rare." (See p 2067, para 1).

Ziober et al. (Lab-on-a-chip for oral cancer screening and diagnosis, 2008, Head and Neck, Vol 30, pp 111-121) also discuss gene expression analysis for diagnosis of cancer, and OSCC in particular, and state: "However, to date, no single gene has shown sufficient diagnostic utility in OSCC. Thus, as in many other cancers, clinical diagnosis will require considering the combined influence of many genes" (emphasis added, see p 114, col 1, para 2). Ziober et al. go on to discuss the state of the art regarding the predictive power of expression profiles and their clinical usefulness:

> "Unfortunately, there are still many questions regarding the identification of various expression profiles, establishing their predictive power, and developing procedures to collect, process, and analyze specific cancer samples and derive clinically useful information utilizing these cancer markers. Synergism from coordinated development of practical lab-on-a-chip systems in parallel and close collaboration with supporting and exploratory biomedical and clinical research would foster progress in both microfluidics technology and cancer diagnostics and therapeutics" (see p 119, col 2, para 2).

Westra et al. (Toward early oral cancer detection using gene expression profiling of saliva: a thoroughfare or a dead end?, 2004, Clinical Cancer Research, Vol 10, pp 8130-8131) also discuss the problems with using gene expression analysis for diagnosis of cancer, particularly in regards to OSCC (throughout document). Westra et al. list some of the issues such as obtaining and validating markers are up-regulated in high-risk tissues, but not normal tissues, and that they must be altered in early stages in cancer development (see p 8130, col 1, para 1). Westra et al. further caution against the use of IL-8 as a specific biomarker of oral cancer because IL-8 levels increase in a variety of oral inflammatory conditions and state:

> "Second, the exclusivity of a gene expression profile for oral neoplasia must first be established before that particular profile is embraced as a "cancer signature." The background frequency of the biomarker must be documented for individuals without oral cancer across a broad range of exposures (*e.g.,* tobacco and alcohol) and nonneoplastic conditions (*e.g.,* dental caries and gingivitis). The enthusiasm for using interleukin (IL)-8, an inflammatory cytokine, as a specific biomarker of oral cancer must be tempered by an awareness that IL-8 levels also increase in a variety of oral inflammatory conditions (5, 6). IL-8 measurement has been advocated as an effective means of monitoring oral disease activity ranging from dental caries to chronic aphthous ulcers to (now) oral carcinoma. Ongoing population-based screening studies that seek to resolve cancer-specific alterations from the background clamor of extraneous variations will ultimately prove indispensable to a more deliberate interpretation of gene expression data. This uncompromising rejection of even a marginal false positive rate has been the downfall of many initially promising attempts to screen for oral cancer.
>
> Third, translational studies that focus on early cancer detection and cancer risk assessment cannot lose sight of oral premalignancies (*i.e.*, oral dysplasia and carcinoma *in situ*), not overt malignancies, as the optimal target of gene expression profiling. Because Li *et al.* (3) did not include premalignancies, effective application of their approach to the arena of oral cancer screening is intriguing but speculative. Cancer-specific expression profiles of clinically apparent carcinomas are diagnostically relevant only to the degree that they are consistently present and measurable in early (*i.e.*, preclinical) stages of tumor progression." (See p 8130, col 2, para 3-4).

Lastly, Squire et al. (Molecular cytogenetic analysis of head and neck sqaumous cell carcinoma: by comparative genomic hybridization, spectral karyotyping, and expression array analysis, 2002, Head and Neck, Vol 24, pp 874-887) teach that while IL-8 was significantly over-expressed in OSCC samples, it was only consistently over-expressed in 3 out of 6 samples (see p 879, col 2, para 2), indicating the variability in IL-8 expression in OSCC samples and the variability in detecting positive correlation using IL-8 expression alone.

Therefor, the level of predictability in the art is dependent on many factors, altered gene expression could correlate with many different diseases, and detection of cancer using a single marker is unreliable. Thus, it is highly unpredictable to use altered expression data for the purpose of specifically diagnosing cancer in any subject.

The level of skill in the art:

The level of skill would be high, most likely at the Ph.D. level.

The amount of direction provided by the inventor and the existence of working examples:

While the applicants provide evidence of increased IL-8 expression in OSCC subjects, these increased levels are not present in all of the subjects (see Fig 5A), and there is no indication of how these changes, alone, would be correlated with diagnosing cancer, or OSCC, in an unknown sample. In addition, there are no working examples of correlating gene expression with any other pathology, disease, or disorder (other than OSCC). The specification only teaches that altered gene/protein expression occurs in some OSCC patients, but does not teach how any one of these could be used to diagnose OSCC, or any other disease, pathology, or disorder in an unknown sample. Therefore, applicants have not provided any data regarding a method of diagnosing OSCC, or any disease, pathology, or disorder.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

In light of the unpredictability surrounding the claimed subject matter, the undue breadth of the claimed invention's intended use, and the lack of adequate guidance, one wishing to practice the presently claimed invention would be unable to do so without engaging in undue experimentation. One wishing to practice the presently claimed invention would have to produce additional experiments to determine how (or if) changes in expression of a single gene could be used to specifically diagnose OSCC in an unknown sample and would have to perform an immeasurable number of experiments to determine how (or if) changes in a single gene could be

used to diagnose any disease, pathology or disorder, including determining what potential genes would even be used.

Response to Arguments

Applicant's arguments filed March 22, 2011 have been fully considered but they are not persuasive for the following reasons. Applicants' arguments are presented in Italics.

Applicants assert that the claims are directed to a diagnostic assay and that the examiner has improperly applied the enablement rejection (Response, p 5).

In response, it is noted that the instant claims are not interpreted as a "diagnostic assay." The instant claims are directed to a method for diagnosing a disease. Methods of diagnosing cancer using gene expression are highly unpredictable, as discussed supra, and particularly when comparing expression levels of a single gene.

"If mere plausibility were the test for enablement under section 112, applicants would obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318.

Applicants assert that the Examiner has taken the position that the instant invention is not enabled based upon its performance and that Sun et al. teach that microarrays may not be superior to conventional methodologies (Response, p 7).

In making this assertion, applicants have very selectively applied the teachings of Sun et al. Firstly, it is acknowledged that Sun et al. do teach advantages of microarrays (e.g.: p 2066, col 2), but teach that its clinical application are questionable for a number of reasons, as discussed supra, including "(b) Most studies had a limited number of cases and an independent validation was not adequately conducted. (c) Current analytic algorithms favor genes at high expression or genes highly differentially expressed, most of which are related to tumor differentiation and may not correlate with clinical outcomes; conversely, genes expressed at low levels or in a subtle difference are often overlooked, which may be quite relevant biologically to clinical questions. (d) There are still some unsolved technical issues about DNA microarray; for example, different microarray platforms (27) or studies from different laboratories using the same platform (28) often produce inconsistent results even when the same RNA samples were used for hybridization. (e) Results from different analytic approaches also differ (23). As an undesirable consequence, consistent or overlapped genes selected for predicting the same outcome from multiple studies are rare." (See p 2067, para 1). Applicants appear to have selectively argued only one of the reasons of Sun et al. relating to clinical usefulness. However, the reference as a whole was relied on to show the unpredictability of using microarrays and gene expression for diagnosing cancer. Therefore, it was not the issue of superior performance that was used as the standard.

It is further noted that applicants appear to have compiled a few select statements from the references cited by the examiner rather than reading them as a whole. For example, while applicants assert that Westra et al. teach that "[t]he work of Li *et al* opens a new avenue for the early detection and intervention of oral cancer" (Response, p 7, para 3), Westra et al., directly

after that sentence, state "However, the road to practical and effective oral cancer screening based on gene expression profiling is a long one, and Li *et al.* (3) brings us only a few small steps further along it. Progress along this road will be ultimately propelled by the identification of biomarkers with a definite specificity for oral neoplasia (inclusive of its early stage) as validated in large populations of individuals without oral cancer, with oral cancer, and at high risk of developing oral cancer" (p 8131, col 1, para 2). Westra et al. also caution against the use of IL-8 as a specific biomarker of oral cancer because IL-8 levels increase in a variety of oral inflammatory conditions, as discussed supra.

Thus, contrary to applicants assertions, the art, when reviewed as a whole (rather than a few select passages), teaches the unpredictability of using gene expression profiles for diagnosis of cancer.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim10, 12-13 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kopreski et al. (US Patent 6607898, filed August 31, 2000), Kopreski et al. (US Patent 6759217, filed September 28, 2001), and Squire et al. (Molecular cytogenetic analysis of head and neck sqaumous cell carcinoma: by comparative genomic hybridization, spectral karyotyping, and expression array analysis, 2002, Head and Neck, Vol 24, pp 874-887). Modifications to the rejection were necessitated by the claim amendments.

Regarding present claims 10, 13, and 28, Kopreski et al. (2000) teach a method for diagnosing cancer, such as head and neck cancer (see claims 1-6), comprising providing a cell free biological sample, such as saliva, detecting extracellular mRNA expression of a gene associated with cancer, such as hTR or hTERT (i.e.: associated with the pathology, disease, or disorder), comparing it to a positive control containing the gene of interest (i.e.: a predetermined mRNA profile of the gene, the predetermined mRNA profile of the gene being indicative of the presence of the pathology, a, or disorder; see entire document, particularly col 1, lns 63+, col 2, lns 1-55, col 3, lns 9-19, 33-50, 60+, col 4, col 6, lns 46-59, clms 1-30).

While Kopreski et al. (2000) teach a method for diagnosing a systemic disease such as cancer by extracting mRNA from cell free fluids such as saliva, Kopreski et al. (2000) do not specifically teach quantitative PCR.

Regarding present claims 10 and 28, Kopreski et al. (2001) also teach a method for diagnosing cancer comprising providing a cell fee biological sample, such as saliva, detecting extracellular mRNA expression of a gene, such as EGF, c-myc, and her-2/neu, and performing

quantitative PCR to enable comparison of the amount of extracellular mRNA present in a sample to the range of amounts of mRNA present in populations with cancer, premalignancy, and populations without cancer (see entire document, particularly col 2, lns 30-64col 8, lns 25-35, col 12, lns 9-16).

While Kopreski et al. (2000) and Kopreski et al. (2001) teach a method for diagnosing a systemic disease such as cancer by extracting mRNA from cell free fluids such as saliva, Kopreski et al. (2000) and Kopreski et al. (2001) do not specifically teach cancer of the oral cavity or IL-8.

Regarding present claims 10 and 12-13, Squire et al. teach a method comprising analyzing gene expression in subjects suffering from head and neck squamous cell carcinoma (HNSCC) of the oral cavity in order to identify regions subject to alterations in gene expression, and further teach upregulation of IL-8 mRNA in HNSCC samples (see entire document, particularly abstract, p 876, col2, last para, p 877, col 1, para 1, p 879, col 2, para 2, Table 4).

Therefor it would have been obvious to one of skill in the art at the time of the invention to mRNA levels by quantitative PCR as taught by Kopreski et al. (2001) and to detect IL-8 levels in OSCC subjects as taught by Squire et al. in the method taught by Kopreski et al. (2000).

One would have been motivated to do so because Kopreski et al. (2001) teach that quantitative PCR can be used to detect mRNA levels and enables comparison to other populations with malignancy, premalignancy, or normal (see col 12, lns 9-16) in order to diagnose cancer and because Squire et al. teach that HNSCC, which encompasses OSCC, is the sixth most common human neoplasm and has low long-term survival (see p 875, col 1, para 1).

One would have had a reasonable expectation for success because Kopreski et al. (2000) and Kopreski et al. (2001) are both directed to detecting extracellular mRNA in samples from subjects in order to diagnose cancer and because Squire et al. also teach correlating up-regulated genes with cancer tissue and that IL-8 was one of five genes consistently up-regulated in OSCC samples (see p 879, col 2, para 2).

Therefor the teachings of Kopreski et al. (2000), Kopreski et al. (2001), and Squire et al. renders the present invention *prima facie* obvious.

In addition, it would have been obvious to one skilled in the art to substitute one known element (i.e.: Quantitative PCR taught by Kopreski et al. (2001) and correlating OSCC with IL-8 as taught by Squire et al.) for another known element (i.e.: methods of detecting, type of cancer, and marker taught by Kopreski et al. (2000)) using known methods (i.e.: the methods taught by all the methods) with no change in their respective functions, and the substitution would have yielded the predictable results of screening for IL-8 in saliva of OSCC patients to one of ordinary skill in the art at the time of the invention. See *KSR International Co. v. Teleflex Inc.*, USPQ2d 1385 (U.S. 2007).

Response to Arguments

Applicant's arguments filed March 22, 2011 have been fully considered but they are not persuasive for the following reasons. Applicants' arguments are presented in Italics.

Applicants assert that none of the cited references teach or suggest that the expression profile observed in cellular fractions is the same as that in non-cellular fractions and that, therefore, there would have been no motivation to look at IL-8 expression (Response, p 11).

In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, all of the cited references are directed to screening/analyzing gene expression in cancer subjects and Squire et al. also teach correlating up-regulated genes with cancer tissue and that IL-8 was one of five genes consistently up-regulated in OSCC samples (see p 879, col 2, para 2). Therefore it is unclear why one wouldn't be motivated to analyze the gene expression of a gene known to be consistently upregulated. Further, it is noted that the instant method, as amended, is not limited to a cell free fraction (e.g.: a saliva sample with cells that have been lysed and filtered out would read on saliva supernatant), in which case one would expect the same expression profile.

In addition, the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). See MPEP § 2145 I.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Future Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHANNON JANSSEN whose telephone number is (571)270-1303. The examiner can normally be reached on Monday-Friday 10:00AM-7:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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